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Hypothesis

# Doxorubicin treatment inhibits PPARγ and may induce lipotoxicity by mimicking a type 2 diabetes-like condition in rodent models

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ABSTRACT

**Doxorubicin-treated animals show elevated serum triglyceride and blood glucose levels. Adipocytes play an important role in buffering blood glucose and lipids. A raise in serum lipid level triggers adipogenesis in order to increase the lipid absorption capacity of adipose tissue. Doxorubicin inhibits adipogenesis through the down-regulation of PPARγ, a crucial component of the lipid metabolic pathway which controls the expression of glucose and fatty acid transporters. Doxorubicin-mediated down-regulation of PPARγ inhibits blood glucose and lipid clearance thereby causing hyperglycemia and hyperlipidemia resulting in lipotoxicity, glucotoxicity, inflammation and insulin resistance. Therefore we hypothesize that doxorubicin treatment could mimic a type 2 diabetic condition.**



## 1. Introduction

Doxorubicin is an anthracyclin antibiotic, commercially prepared from *Strepotmyces peucetius* var. *caesius* [1]. It is effective against a wide spectrum of cancers ranging from solid tumors to leukemia and lymphoma. Cancers treated with doxorubicin include: bladder, breast, head and neck, leukemia, liver, lung, lymphomas, mesothelioma, multiple myeloma, neuroblastoma, ovary, pancreas, prostate, sarcomas, stomach, testis, thyroid and uterus cancer.

Side effects of doxorubicin include vomiting, male infertility, cardiotoxicity, mouth sores, nausea, vomiting, diarrhea, fast or irregular heartbeats, unusual bleeding or bruising black or tarry stools, or blood in stools or urine, extreme fatigue, swelling of the feet or ankles. The congestive cardiomyopathy is the most severe side effect of doxorubicin limiting its therapeutic utility.

The mechanism of action of doxorubicin is yet not clear and still under investigation. However, Fornari et al. [2] explained that doxorubicin interact with DNA by intercalation. This interaction results in interruption of macromolecular biosynthesis [3], leading to modulation in the expression of a number of genes and thereby inhibiting tumor progression. Previously, we explained the possible mechanism that may be involved in doxorubicin induced spermatogenesis defect [4]. In this report, we explain how doxorubicin causes disturbance in glucose and lipid buffering abilities of adipocyte which may mimic type 2 diabetes like condition.

## 2. Doxorubicin affects body weight, blood glucose and serum lipid profile mimicking type 2 diabetic condition

Along with other side effects, many studies reported that doxorubicin treatment affects body weight; 2.5 mg/kg body weight of doxorubicin by intravenous injection once a week for consecutive 6 weeks significantly reduced the body weight of animals compared to control [5]. Earlier studies reported that 1.25 mg/kg body weight of doxorubicin interaperitoneal injection prevented the gain of body weight compared to controls [6,7]. Apart from other possible factors, the weight loss could be due to the loss of adipose tissue induced by doxorubicin [8,9].

Also, studies on rodent models demonstrated that doxorubicin treatment increases serum total cholesterol, triglyceride and LDL cholesterol levels when compared with the control group [10–12]. It was also observed that the total fatty acids, especially C16–C18 fatty acids, were significantly elevated after injection of ADR [13]. Doxorubicin treatment also showed an increase in blood glucose and glycogen levels [14].

Accumulating evidences from both animal and human studies shown hyperlipidemia [15,16] raised TG/HDL ratio along with high

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level of fasting blood glucose [17,18] as a condition of type 2 diabetes. Elevated TG/HDL and hyperlipidemia might be due to non-absorption of lipids and glucose by adipocytes and muscle cells which might be due to the down-regulation of PPARγ.

## 3. PPARγ is essential for glucose and lipid clearance

Peroxisome proliferator activated receptor gamma (PPARγ) plays a crucial role in the clearance of serum triglyceride as well as blood glucose. Studies in rodent models showed that PPARγ agonists robustly reduce circulating triglycerides (TG) [19–22]. The PPARγ agonists reduce the serum triglyceride level by supporting the intravascular hydrolysis of triglyceride rich lipoproteins via increased lipoprotein lipase expression or activity and subsequently by promoting the fatty acid uptake in white adipose tissue (WAT) [23,24]. Blood glucose clearance on the other hand is also managed by PPARγ, via regulating the glucose transporters [25]. PPARγ stimulation improves glucose tolerance and insulin sensitivity in type 2 diabetic patients and in animal models of insulin resistance [26]. *In vitro* studies on 3T3-L1 adipocytes showed that suppression of PPARγ reduces insulin stimulated glucose uptake without affecting the early insulin signaling steps in the adipocytes [27] due to insufficient activity of GLUT4 [28].

PPARγ is normally expressed prominently in white adipose tissue, with much lower levels in liver and skeletal muscle [29–31]. Fatless mice showed higher expression of PPARγ in liver with high level of hepatic triglyceride resembling a steatosis condition. In this fatless condition it was unclear that the PPARγ higher expression is correlated with increased lipid uptake or increased lipogenesis. However, in animal models of steatosis fed with methionine choline deficient diet, it was observed that the animals had a reduced gonadal as well as subcutaneous fat, and higher hepatic lipid accumulation. The author suggested a higher uptake of lipids and reduced lipogenesis. It could be possible that, in the absence of adipose tissue, the liver overtakes the trade of adipose tissue. This could be the reason due to which the expression of PPARγ is high in the liver of animals with absence of adipose tissue either genetically or pathologically [32–34]. Taking all this together, it can be concluded that PPARγ is essential for the uptake of blood glucose as well as serum lipid clearance.

On the other hand, some studies also show that, partially reducing the PPARγ expression either genetically [35] or using an antagonist [36] increased the insulin sensitivity. The same follows for PPARα also [37]. PPARγ along with other nuclear transcription factors including PPARα shares a common binding partner known as retinoid X receptor [RXR] required for the transition of these nuclear receptors from cytoplasm to nucleus [38]. The existence of either PPARγ or PPARα at lower concentration increases the chances of the other one to bind with RXR and upregulate the gene expression controlled by the one which is at a higher concentration. The PPARα null animals develop increased adiposity in response to a high-fat diet but were protected from the development of insulin resistance; due to the absence of PPARα it could be possible that PPARγ–RXR union was high resulting in the higher transition of PPARγ from the cytoplasm to the nucleus leading to increased imports of glucose and lipids to the adipocytes and liver. Another study [39] indicates that adipose tissue specific PPARγ knock out animals were protected against high fat diet-induced obesity and insulin resistance. But these animals showed a marked reduction in glucose uptake in skeletal muscle, similar to that of the insulin resistant controls, however, this was compensated by increased glucose and lipid uptake by liver showing a higher expression of hepatic PPARγ. The liver weight and triglyceride content of adipose tissue specific PPARγ knock-out animals were higher than the control counterpart. We did not find any study indicating inhibition of PPARγ and α together either chemically or genetically, suggesting that, suppression of both of these PPARs together could be deleterious. However, upregulation of both the PPARs together using dual agonist was found to be beneficial in improving both lipid and glucose homeostasis [40].

In this current paper all the reports we discussed, in which animals were treated with doxorubicin did neither shown a reduction in serum triglyceride nor an increase in adipose or non-adipose tissue weight, which indicates that the lipid and glucose import regulated by PPARγ was severely disturbed due to PPARγ inhibition, although there is no existing evidence on the expression pattern of PPARα on liver or adipocyte of doxorubicin treated animal, however, studies [41] on cultured podocytes indicated that doxorubicin treatment reduces the expression of PPARα. Collectively, it can be concluded that doxorubicin disturbs the lipid metabolic process by inhibition of PPARγ and α, though there is no strong evidence for PPARα, but it can be postulated based on the observational parameters.

## 4. The correlation between PPARγ and adipose tissue mass

PPARs are group of nuclear receptor super family that acts as transcription factors. PPARγ is expressed 10- to 30-fold higher in adipose tissue than any other tissues [29], apart from other roles, PPARγ plays a crucial role in adipogenesis [42] and increases insulin sensitivity when it is activated by thiazolidinediones (TZD) [43–45]. PPARγ mutation fails to induce adipogenesis and causes insulin resistance [46].

TZDs are a group of PPARγ agonists used in the treatment of type 2 diabetes. Treating diabetic animals with PPARγ agonists induces weight gain in most studies [34,47–49], while reducing the expression of PPARγ causes weight loss in animal models. GW9662, an antagonist of PPARγ, inhibits adipogenesis [50]. Examination of body weight and fat composition in animals fed with high fat diet along with GW9662 showed that the animals were protected from weight gain due to a reduction in visceral adipose tissue mass [36].

FAT/CD36 has been shown to be transporting long chain fatty acids across the plasma membrane during adipocyte differentiation [51]. A number of evidences prove that expression of FAT/CD36 is directly regulated by PPARγ [52]. Similarly, other fatty acid transporters like lipoprotein lipase (LPL) [53], fatty acid transport protein (FATP) and adipocyte fatty acid binding protein (A-FABP) are regulated by PPARγ [54]. Therefore, suppressing the expression of PPARγ would cause reduction in adipose tissue mass along with agitation in the functioning of fatty acid transporters leading to a decline in the rate of clearance of circulating fatty acids and glucose.

## 5. Role of PPARγ in lipotoxicity and glucotoxicity

It has been reported that ablation of PPARγ-2 in the ob/ob background, PPARγ$^{2-/-}$ Lepob/Lepob (POKO mouse), resulted in decreased fat mass along with severe insulin resistance, β-cell failure and dyslipidemia [55]. PPARγ-2 isoform plays an important role, mediating adipose tissue expansion in response to positive energy balance. PPARγ-2 isoform prevents lipotoxicity by promoting adipose tissue expansion, increasing the lipid-buffering capacity of peripheral organs, and facilitating the adaptive proliferative response of β-cells to insulin resistance.

Both *in vivo* and *in vitro* studies revealed the importance of PPARγ in lowering the glucotoxicity [55,56]. Clonal pancreatic BRIN-BD11 β-cells when maintained in standard, glucotoxic and lipotoxic cultures caused a reduction in the cellular viability, however, when these cells were exposed to the PPARγ agonist

rosiglitazone, a significant improvement of many of the adverse effects of gluco- and lipo-toxic conditions on insulin secretory responsiveness were observed [56]. In another study on Zucker diabetic fatty rat, it was observed that PPARγ agonist TZD prevent glucotoxic effects [57]. These studies indicate that PPARγ is very crucial in glucose and lipid metabolism and drastic down-regulation of this gene may result in severe gluco- and lipo-toxicities.

## 6. Role of lipotoxicity in diabetes

Lipotoxicity refers to a condition where there is an accumulation of excess lipids in non-adipose tissues leading to cell dysfunction or cell death. Lipotoxicity plays an important role in the pathogenesis of diabetes and heart failure in humans [58]. In lipotoxic state the fatty acid spillover is excess of the oxidative needs, resulting in enhanced metabolic flux leading to harmful pathways of non-oxidative metabolism [59]. In normal physiological condition, cellular fatty acid homeostasis reflects a balance between processes that generate or deliver fatty acids and processes that utilize these molecules. In mammalian cells, free fatty acids (FFAs) are generated through the *de novo* synthesis pathway and liberated as a result of triglycerides and phospholipids hydrolysis by cellular lipases. Raise in plasma FFA and triglyceride level triggers import of FFAs into non-adipose tissues contributing to intracellular lipid accumulation.

Accumulating evidence suggests a strong association between altered fat topography and defects in adipocyte metabolism with the pathogenesis of type 2 diabetes [60]. Extensive import of lipid raises the lipid overload condition in pancreatic β-cells leading to deregulated insulin secretion with shorter chronic reduction in insulin levels [61–63]. In addition to FFA-induced β-cell dysfunction, accumulation of excess FFAs also causes β-cell apoptosis. In animal model it was observed that triglyceride accumulation in islets was associated with reductions in β-cell mass and declining insulin production [64].

## 7. Inflammation as a precursor of insulin resistance

As we described, the rise in plasma FFA induces lipotoxicity. This rise in plasma free fatty acids could be because of the inability of adipocytes and muscle cells to absorb them due to the down-regulation of PPARγ which itself is an insulin resistance condition. These circulating FFAs recruit macrophages into the adipose tissue [65]. FFAs activate nuclear factor kB (NF-kB) in macrophages through toll-like receptor 2 and 4 [66]. Translocation of NF-kB to the nucleus, allows transcription of genes involved in the

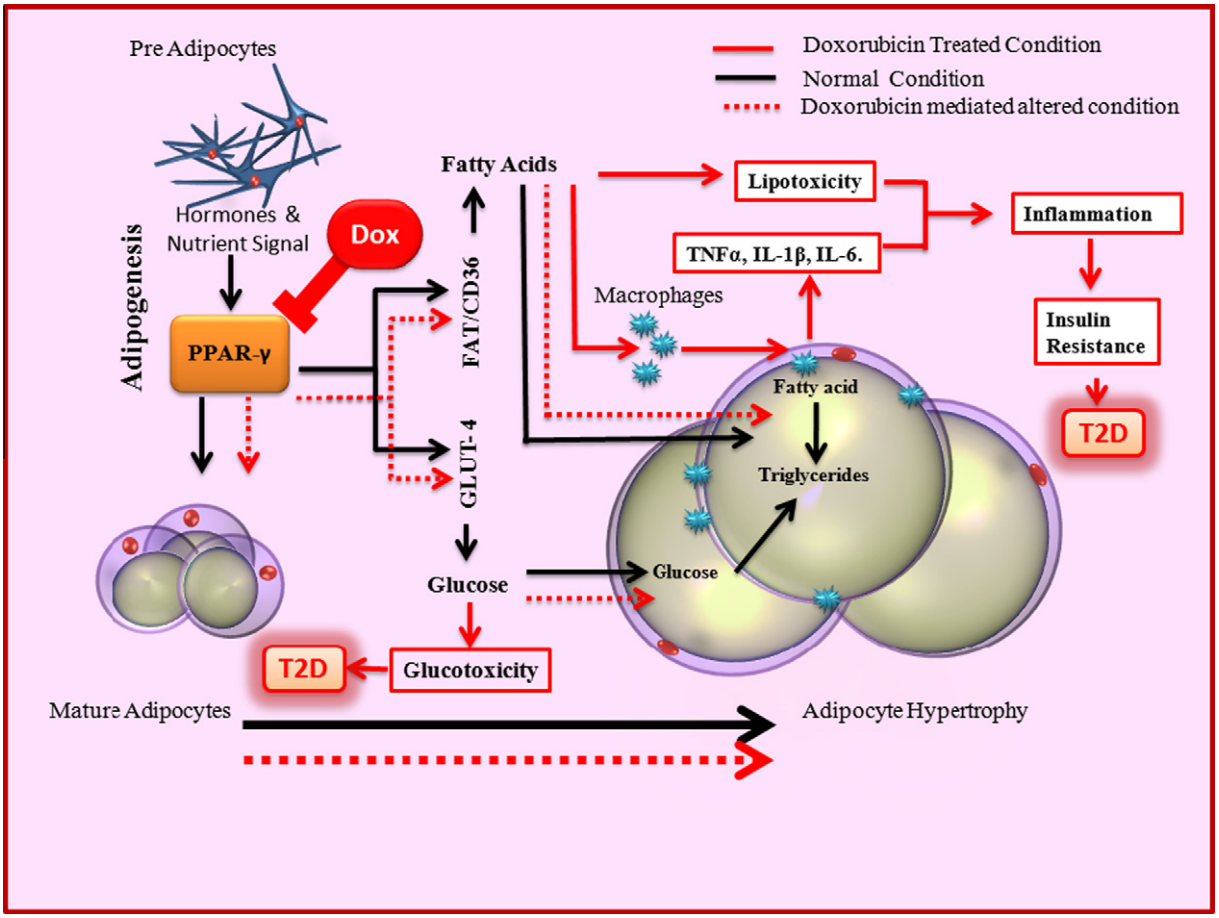


**Fig. 1.** The possible effect of Doxorubicin induced disturbance in adipocyte physiology. Doxorubicin (DOX) inhibits the expression of PPARγ (Peroxisome proliferator-activated receptor *gamma*) leading to suppression of adipogenesis. Therefore, no new mature adipocyte will form from the pre-adipocytes. Secondly the existing adipocyte will have low expression of PPARγ resulting in the impaired import of glucose and free fatty acids mediated through GLUT4 (Glucose transporter type 4) and FAT/CD36 (Fatty acid transport protein/Cluster of Differentiation 36) respectively in the adipose tissue. Increased level of circulating fatty acid and glucose will lead to lipotoxicity and glucotoxicity. Elevated circulating free fatty acids would cause infiltration of macrophage into adipose tissue and release of pro-inflammatory cytokines like TNF-α (Tumor Necrosis Factor-alpha), IL-6 (Interleukin-6), IL-1β (Interleukin-1 beta), etc. Secretion of pro-inflammatory cytokines recruit more macrophages leading to insulin resistance and T2D (Type 2 diabetes) like conditions. The black arrows represent mechanisms under normal conditions whereas the red arrows represent the disturbed mechanism resulting from doxorubicin treatment (red dotted lines indicate the interrupted process, red bold lines indicate occurring/ongoing process).

inflammatory response. Consequently, recruited macrophages secrete a variety of pro-inflammatory cytokines like TNFα, IL-1β and IL-6 [67]. Secretion of these pro-inflammatory cytokines further worsens the condition by recruiting more macrophages. Neels and Olefsky [68] suggested that during a variety of insulin-resistant states inflammatory pathway is triggered in adipose tissues. Inflammation of adipose tissue results in deleterious effects on insulin action in these tissues. Recently, it has been shown that anti-inflammatory drugs prevent the fat mediated insulin resistance, suggesting the involvement of inflammatory pathways in the pathogenesis of fat-induced insulin resistance [69,70].

## 8. Adipose tissue and diabetes

Studies using fatless mice (A-ZIP/F) illustrated the importance of adipose tissue in averting diabetes. Fatless mice are severely prone to insulin resistance and show defective insulin signaling in the liver and muscles. Kim et al. [71] reported that, the fatless mice had defects in insulin mediated activation of insulin receptor substrate-1 and -2-associated phosphatidylinositol 3-kinase activity and a 2-fold increase in the muscle and liver triglyceride content. Also, insulin-stimulated glucose transport activity in skeletal muscles was significantly decreased in the fatless mice. Reduction in insulin stimulated glucose transport activity in skeletal muscle has been shown to be a major contributing factor to the insulin resistance in patients with type 2 diabetes [72].

Gavrilova et al. have shown that, transplantation of wild adipose tissue improves insulin sensitivity in insulin resistant fatless mice [73]. Adipose tissue can exert anti-diabetic action either via endocrine mechanisms possibly by secretion of leptin [74] or TNF-α [75], both of which affect insulin sensitivity; or via metabolism which include the adipose tissue uptake of glucose, triglyceride, and/or FFA. Animals with transplanted adipose tissue showed low level of glucose, insulin, FFAs and triglyceride level compared with the control indicating the importance of adipose tissue in maintaining the glucose and lipid homeostasis.

## 9. Effect of doxorubicin on adipocyte physiology

We have recently reported that a brief exposure (3 h) of doxorubicin to pre-adipocytes inhibited adipogenesis in a dose-dependent manner [76]. While investigating the reason behind, we found that doxorubicin down-regulates the expression of PPARγ in a dose dependent manner. Searching for changes in the upstream element of PPARγ, one more gene, KLF4 was found to be downregulated. KLF4 has been shown to be the earliest member of adipogenic pathway which responds to adipogenic signal as early as 30 min [77]. In an earlier report doxorubicin has been shown to be antagonistic to KLF4 [78]. As a result of inhibition of KLF4 its downstream elements like CEBPβ and PPARγ have also been shown to be down-regulated by doxorubicin which ultimately leads to the lack of fat accumulation. These two genes play crucial role in inducing adipogenesis. Down-regulation of PPARγ affects the expandability and adipogenesis of adipocytes. Others' study indicated loss of adipose tissue in doxorubicin treated animals [8,9].

## 10. Hypothesis

From the existing literature it can be realized that doxorubicin affects the physiology of adipocytes via disturbing the expression of PPARγ. The down-regulation of PPARγ would possibly affect the lipid and glucose metabolism directly (Fig. 1).

Adipose tissue plays major role in lipid and glucose uptake. The doxorubicin mediated downregulation of PPARγ expression might inhibit the expression of glucose and lipid transporters leading to the inability of adipose tissue to absorb glucose and lipids. Normally, raise in serum lipid level triggers adipogenesis in order to expand the lipid absorption capacity of adipose tissue to maintain a normal blood lipid profile. But in doxorubicin treated case this expandability of adipose tissue will be lost; therefore, raise in blood glucose and triglyceride levels will lead to many disorders, and will mimic a state of insulin resistance or type 2 diabetes. This condition will further cause glucotoxicity and lipotoxicity.

## 11. Conclusion

It can be assumed that doxorubicin treatment might cause two possible conditions; first the existing adipocytes will not be able to absorb the serum glucose and lipids; second, the adipogenesis triggered by circulating glucose and lipid will be inhibited. Thus, the pre-adipocytes differentiation to adipocyte and expansion of mature adipocyte by the uptake of circulating serum lipid and glucose would be interrupted. In the absence of adipose tissue, liver absorbs most of the serum triglyceride via PPARγ regulated pathway. There is no existing evidence whether or not PPARγ is down-regulated in liver of doxorubicin treated animal. But it could be possible that apart from adipose tissue hepatic PPARγ may also get inhibited, reducing the chances of serum lipid clearance even by lipid disposing peripheral organs. This situation could result in the rise of circulating serum triglyceride and glucose, because of the reduced capacity of adipocytes and other peripheral organs to uptake the circulating triglyceride as well as glucose, resulting in glucotoxicity , lipotoxicity and insulin resistance status. This condition is further worsened by the recruitment of macrophages to the adipose tissue which triggers inflammation of adipose tissue. Inflamed adipose tissue responds poorly to the insulin signaling which mimics the type 2 diabetic condition.

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## References

[1] Di Marco, A., Gaetani, M. and Scarpinato, B. (1969) Adriamycin (NSC-123,127): a new antibiotic with antitumor activity. Cancer Chemother. Rep. 53, 33–37.
[2] Fornari, F.A., Randolph, J.K., Yalowich, J.C., Ritke, M.K. and Gewirtz, D.A. (1994) Interference by doxorubicin with DNA unwinding in MCF-7 breast tumor cells. Mol. Pharmacol. 45, 649–656.
[3] Momparler, R.L., Karon, M., Siegel, S.E. and Avila, F. (1976) Effect of adriamycin on DNA, RNA, and protein synthesis in cell-free systems and intact cells. Cancer Res. 36, 2891–2895.
[4] Tirupathi Pichiah, P.B. et al. (2012) Adriamycin induced spermatogenesis defect is due to the reduction in epididymal adipose tissue mass: a possible hypothesis. Med. Hypotheses 78, 218–220.
[5] Xiang, P. et al. (2009) Dexrazoxane protects against doxorubicin-induced cardiomyopathy: upregulation of Akt and Erk phosphorylation in a rat model. Cancer Chemother. Pharmacol. 63, 343–349.
[6] Kelishomi, R.B., Ejtemaeemehr, S., Tavangar, S.M., Rahimian, R., Mobarakeh, J.I. and Dehpour, A.R. (2008) Morphine is protective against doxorubicin-induced cardiotoxicity in rat. Toxicology 243, 96–104.
[7] Santos, R.V., Batista Jr., M.L., Caperuto, E.C. and Costa Rosa, L.F. (2007) Chronic supplementation of creatine and vitamins C and E increases survival and improves biochemical parameters after Doxorubicin treatment in rats. Clin. Exp. Pharmacol. Physiol. 34, 1294–1299.
[8] Xu, Y., Liu, Z., Sun, J., Pan, Q., Sun, F., Yan, Z. and Hu, X. (2011) Schisandrin B prevents doxorubicin-induced chronic cardiotoxicity and enhances its anticancer activity in vivo. PLoS ONE 6, e28335.
[9] El-Sayyad, H.I., Ismail, M.F., Shalaby, F.M., Abou-El-Magd, R.F., Gaur, R.L., Fernando, A., Raj, M.H. and Ouhtit, A. (2009) Histopathological effects of cisplatin, doxorubicin and 5-flurouracil (5-FU) on the liver of male albino rats. Int. J. Biol. Sci. 5, 466–473.
[10] Koti, B.C., Vishwanathswamy, A.H., Wagawade, J. and Thippeswamy, A.H. (2009) Cardioprotective effect of lipistat against doxorubicin induced myocardial toxicity in albino rats. Indian J. Exp. Biol. 47, 41–46.

[11] Iliskovic, N. and Singal, P.K. (1997) Lipid lowering: an important factor in preventing adriamycin-induced heart failure. Am. J. Pathol. 150, 727–734.
[12] Venkatesan, N., Venkatesan, P., Karthikeyan, J. and Arumugam, V. (1997) Protection by taurine against adriamycin-induced proteinuria and hyperlipidemia in rats. Proc. Soc. Exp. Biol. Med. 215, 158–164.
[13] Hong, Y.M., Kim, H.S. and Yoon, H.R. (2002) Serum lipid and fatty acid profiles in adriamycin-treated rats after administration of L-carnitine. Pediatr. Res. 51, 249–255.
[14] Geetha, A., Catherine, J. and Shyamala Devi, C.S. (1989) Effect of α-tocopherol on doxorubicin induced alterations in glucose metabolism—A pilot study. J. Biosci. 14, 243–247.
[15] Khan, S.R., Ayub, N., Nawab, S. and Shamsi, T.S. (2008) Triglyceride profile in dyslipidaemia of type 2 diabetes mellitus. J. Coll. Physicians Surg. Pak. 18, 270–273.
[16] Solano, Maria P. and Goldberg, Ronald B. (2006) Lipid management in type 2 diabetes. Clin. Diabetes 24, 6.
[17] Gordon, L., Ragoobirsingh, D., Morrison, E.Y., Choo-Kang, E., McGrowder, D. and Martorell, E. (2010) Lipid profile of type 2 diabetic and hypertensive patients in the Jamaican population. J. Lab. Physicians 2, 25–30.
[18] Sapna, S. and Alok, M.L. (2008) A study on lipid profile levels of diabetics and non-diabetics among Naini Region of Allahabad, India. Turk. J. Biochem 33, 4.
[19] Jiang, G. et al. (2002) Potentiation of insulin signaling in tissues of Zucker obese rats after acute and long-term treatment with PPARgamma agonists. Diabetes 51, 2412–2419.
[20] Laplante, M., Sell, H., MacNaul, K.L., Richard, D., Berger, J.P. and Deshaies, Y. (2003) PPAR-gamma activation mediates adipose depot-specific effects on gene expression and lipoprotein lipase activity: mechanisms for modulation of postprandial lipemia and differential adipose accretion. Diabetes 52, 291–299.
[21] Oakes, N.D., Thalen, P.G., Jacinto, S.M. and Ljung, B. (2001) Thiazolidinediones increase plasma-adipose tissue FFA exchange capacity and enhance insulin-mediated control of systemic FFA availability. Diabetes 50, 1158–1165.
[22] Olivecrona, T. (1962) The metabolism of 1-$C^{14}$-palmitic acid labeled chylomicrons in rats. Acta Physiol. Scand. 55, 170–176.
[23] Lefebvre, A.M. et al. (1997) Regulation of lipoprotein metabolism by thiazolidinediones occurs through a distinct but complementary mechanism relative to fibrates. Arterioscler. Thromb. Vasc. Biol. 17, 1756–1764.
[24] McTernan, P.G. et al. (2002) Insulin and rosiglitazone regulation of lipolysis and lipogenesis in human adipose tissue in vitro. Diabetes 51, 1493–1498.
[25] Wahli, W., Braissant, O. and Desvergne, B. (1995) Peroxisome proliferator activated receptors: transcriptional regulators of adipogenesis, lipid metabolism and more. Chem. Biol. 2, 261–266.
[26] Picard, F. and Auwerx, J. (2002) PPAR(gamma) and glucose homeostasis. Annu. Rev. Nutr. 22, 167–197.
[27] Liao, W., Nguyen, M.T., Yoshizaki, T., Favelyukis, S., Patsouris, D., Imamura, T., Verma, I.M. and Olefsky, J.M. (2007) Suppression of PPAR-gamma attenuates insulin-stimulated glucose uptake by affecting both GLUT1 and GLUT4 in 3T3-L1 adipocytes. Am. J. Physiol. Endocrinol. Metab. 293, E219–27.
[28] Wu, Z., Xie, Y., Morrison, R.F., Bucher, N.L. and Farmer, S.R. (1998) PPARgamma induces the insulin-dependent glucose transporter GLUT4 in the absence of C/EBPalpha during the conversion of 3T3 fibroblasts into adipocytes. J. Clin. Invest. 101, 22–32.
[29] Tontonoz, P., Hu, E., Graves, R.A., Budavari, A.I. and Spiegelman, B.M. (1994) MPPAR gamma 2: tissue-specific regulator of an adipocyte enhancer. Genes Dev. 8, 1224–1234.
[30] Vidal-Puig, A., Jimenez-Linan, M., Lowell, B.B., Hamann, A., Hu, E., Spiegelman, B., Flier, J.S. and Moller, D.E. (1996) Regulation of PPAR gamma gene expression by nutrition and obesity in rodents. J. Clin. Invest. 97, 2553–2561.
[31] Kruszynska, Y.T., Mukherjee, R., Jow, L., Dana, S., Paterniti, J.R. and Olefsky, J.M. (1998) Skeletal muscle peroxisome proliferator-activated receptor-gamma expression in obesity and non-insulin-dependent diabetes mellitus. J. Clin. Invest. 101, 543–548.
[32] Simha, V. and Garg, A. (2006) Lipodystrophy: lessons in lipid and energy metabolism. Curr. Opin. Lipidol. 17, 162–169.
[33] Rinella, M.E., Elias, M.S., Smolak, R.R., Fu, T., Borensztajn, J. and Green, R.M. (2008) Mechanisms of hepatic steatosis in mice fed a lipogenic methionine choline-deficient diet. J. Lipid Res. 49, 1068–1076.
[34] Chao, L., Marcus-Samuels, B., Mason, M.M., Moitra, J., Vinson, C., Arioglu, E., Gavrilova, O. and Reitman, M.L. (2000) Adipose tissue is required for the antidiabetic, but not for the hypolipidemic, effect of thiazolidinediones. J. Clin. Invest. 106, 1221–1228.
[35] Miles, P.D., Barak, Y., He, W., Evans, R.M. and Olefsky, J.M. (2000) Improved insulin-sensitivity in mice heterozygous for PPAR-gamma deficiency. J. Clin. Invest. 105, 287–292.
[36] Nakano, R., Kurosaki, E., Yoshida, S., Yokono, M., Shimaya, A., Maruyama, T. and Shibasaki, M. (2006) Antagonism of peroxisome proliferator-activated receptor gamma prevents high-fat diet-induced obesity in vivo. Biochem. Pharmacol. 72, 42–52.
[37] Guerre-Millo, M. et al. (2001) PPAR-alpha-null mice are protected from high-fat diet-induced insulin resistance. Diabetes 50, 2809–2814.
[38] Desvergne, B. and Wahli, W. (1999) Peroxisome proliferator-activated receptors: nuclear control of metabolism. Endocr. Rev. 20, 649–688.
[39] Jones, J.R. et al. (2005) Deletion of PPARgamma in adipose tissues of mice protects against high fat diet-induced obesity and insulin resistance. Proc. Natl. Acad. Sci. USA 102, 6207–6212.
[40] Lecka-Czernik, B. (2010) Aleglitazar, a dual PPARalpha and PPARgamma agonist for the potential oral treatment of type 2 diabetes mellitus. IDrugs 13, 793–801.
[41] Zhou, Y. et al. (2011) Peroxisome proliferator-activated receptor-alpha is renoprotective in doxorubicin-induced glomerular injury. Kidney Int. 79, 1302–1311.
[42] Tontonoz, P., Hu, E. and Spiegelman, B.M. (1994) Stimulation of adipogenesis in fibroblasts by PPAR gamma 2, a lipid-activated transcription factor. Cell 79, 1147–1156.
[43] Frias, J.P., Yu, J.G., Kruszynska, Y.T. and Olefsky, J.M. (2000) Metabolic effects of troglitazone therapy in type 2 diabetic, obese, and lean normal subjects. Diabetes Care 23, 64–69.
[44] Miyazaki, Y. et al. (2001) Improved glycemic control and enhanced insulin sensitivity in type 2 diabetic subjects treated with pioglitazone. Diabetes Care 24, 710–719.
[45] Nolan, J.J., Ludvik, B., Beerdsen, P., Joyce, M. and Olefsky, J. (1994) Improvement in glucose tolerance and insulin resistance in obese subjects treated with troglitazone. N. Engl. J. Med. 331, 1188–1193.
[46] Agostini, M. et al. (2006) Non-DNA binding, dominant-negative, human PPARgamma mutations cause lipodystrophic insulin resistance. Cell Metab. 4, 303–311.
[47] Yakubu-Madus, F.E., Stephens, T.W. and Johnson, W.T. (2000) Lipid lowering explains the insulin sensitivity enhancing effects of a thiazolidinedione, 5-(4-(2-(2-phenyl-4-oxazolyl)ethoxy)benzyl)-2,4 thiazolidinedione. Diabetes Obes. Metab. 2, 155–163.
[48] de Souza, C.J., Eckhardt, M., Gagen, K., Dong, M., Chen, W., Laurent, D. and Burkey, B.F. (2001) Effects of pioglitazone on adipose tissue remodeling within the setting of obesity and insulin resistance. Diabetes 50, 1863–1871.
[49] Yamauchi, T. et al. (2001) The mechanisms by which both heterozygous peroxisome proliferator-activated receptor gamma (PPARgamma) deficiency and PPARgamma agonist improve insulin resistance. J. Biol. Chem. 276, 41245–41254.
[50] Wright, H.M., Clish, C.B., Mikami, T., Hauser, S., Yanagi, K., Hiramatsu, R., Serhan, C.N. and Spiegelman, B.M. (2000) A synthetic antagonist for the peroxisome proliferator-activated receptor gamma inhibits adipocyte differentiation. J. Biol. Chem. 275, 1873–1877.
[51] Abumrad, N.A., el-Maghrabi, M.R., Amri, E.Z., Lopez, E. and Grimaldi, P.A. (1993) Cloning of a rat adipocyte membrane protein implicated in binding or transport of long-chain fatty acids that is induced during preadipocyte differentiation. Homology with human CD36. J. Biol. Chem. 268, 17665–17668.
[52] Lim, H.J., Lee, S., Lee, K.S., Park, J.H., Jang, Y., Lee, E.J. and Park, H.Y. (2006) PPARgamma activation induces CD36 expression and stimulates foam cell like changes in rVSMCs. Prostaglandins Other Lipid Mediat. 80, 165–174.
[53] Schoonjans, K., Peinado-Onsurbe, J., Lefebvre, A.M., Heyman, R.A., Briggs, M., Deeb, S., Staels, B. and Auwerx, J. (1996) PPARalpha and PPARgamma activators direct a distinct tissue-specific transcriptional response via a PPRE in the lipoprotein lipase gene. EMBO J. 15, 5336–5348.
[54] Lemberger, T., Desvergne, B. and Wahli, W. (1996) Peroxisome proliferator-activated receptors: a nuclear receptor signaling pathway in lipid physiology. Annu. Rev. Cell Dev. Biol. 12, 335–363.
[55] Medina-Gomez, G. et al. (2007) PPAR gamma 2 prevents lipotoxicity by controlling adipose tissue expandability and peripheral lipid metabolism. PLoS Genet. 3, e64.
[56] Irwin, N., McKinney, J.M., Bailey, C.J., McClenaghan, N.H. and Flatt, P.R. (2011) Acute and long-term effects of peroxisome proliferator-activated receptor-gamma activation on the function and insulin secretory responsiveness of clonal beta-cells. Horm. Metab. Res. 43, 244–249.
[57] Harmon, J.S., Gleason, C.E., Tanaka, Y., Oseid, E.A., Hunter-Berger, K.K. and Robertson, R.P. (1999) In vivo prevention of hyperglycemia also prevents glucotoxic effects on PDX-1 and insulin gene expression. Diabetes 48, 1995–2000.
[58] Schaffer, J.E. (2003) Lipotoxicity: when tissues overeat. Curr. Opin. Lipidol. 14, 281–287.
[59] Unger, R.H. and Zhou, Y.T. (2001) Lipotoxicity of beta-cells in obesity and in other causes of fatty acid spillover. Diabetes 50 (Suppl. 1), S118–S121.
[60] DeFronzo, R.A. (2004) Dysfunctional fat cells, lipotoxicity and type 2 diabetes. Int. J. Clin. Pract. Suppl., 9–21.
[61] Zhou, Y.P. and Grill, V. (1995) Long term exposure to fatty acids and ketones inhibits B-cell functions in human pancreatic islets of Langerhans. J. Clin. Endocrinol. Metab. 80, 1584–1590.
[62] Prentki, M., Vischer, S., Glennon, M.C., Regazzi, R., Deeney, J.T. and Corkey, B.E. (1992) Malonyl-CoA and long chain acyl-CoA esters as metabolic coupling factors in nutrient-induced insulin secretion. J. Biol. Chem. 267, 5802–5810.
[63] Clayton, P.T. et al. (2001) Hyperinsulinism in short-chain L-3-hydroxyacyl-CoA dehydrogenase deficiency reveals the importance of beta-oxidation in insulin secretion. J. Clin. Invest. 108, 457–465.
[64] Unger, R.H. and Orci, L. (2001) Diseases of liporegulation: new perspective on obesity and related disorders. FASEB J. 15, 312–321.
[65] Shi, H., Kokoeva, M.V., Inouye, K., Tzameli, I., Yin, H. and Flier, J.S. (2006) TLR4 links innate immunity and fatty acid-induced insulin resistance. J. Clin. Invest. 116, 3015–3025.
[66] Nguyen, M.T. et al. (2007) A subpopulation of macrophages infiltrates hypertrophic adipose tissue and is activated by free fatty acids via toll-like receptors 2 and 4 and JNK-dependent pathways. J. Biol. Chem. 282, 35279–35292.

[67] Cusi, K. (2010) The role of adipose tissue and lipotoxicity in the pathogenesis of type 2 diabetes. Curr. Diab. Rep. 10, 306–315.
[68] Neels, J.G. and Olefsky, J.M. (2006) Inflamed fat: what starts the fire? J. Clin. Invest. 116, 33–35.
[69] Yin, M.J., Yamamoto, Y. and Gaynor, R.B. (1998) The anti-inflammatory agents aspirin and salicylate inhibit the activity of I(kappa)B kinase-beta. Nature 396, 77–80.
[70] Yuan, M., Konstantopoulos, N., Lee, J., Hansen, L., Li, Z.W., Karin, M. and Shoelson, S.E. (2001) Reversal of obesity- and diet-induced insulin resistance with salicylates or targeted disruption of Ikkbeta. Science 293, 1673–1677.
[71] Kim, J.K., Gavrilova, O., Chen, Y., Reitman, M.L. and Shulman, G.I. (2000) Mechanism of insulin resistance in A-ZIP/F-1 fatless mice. J. Biol. Chem. 275, 8456–8460.
[72] Cline, G.W. et al. (1999) Impaired glucose transport as a cause of decreased insulin-stimulated muscle glycogen synthesis in type 2 diabetes. N. Engl. J. Med. 341, 240–246.
[73] Gavrilova, O. et al. (2000) Surgical implantation of adipose tissue reverses diabetes in lipoatrophic mice. J. Clin. Invest. 105, 271–278.
[74] Kamohara, S., Burcelin, R., Halaas, J.L., Friedman, J.M. and Charron, M.J. (1997) Acute stimulation of glucose metabolism in mice by leptin treatment. Nature 389, 374–377.
[75] Uysal, K.T., Wiesbrock, S.M., Marino, M.W. and Hotamisligil, G.S. (1997) Protection from obesity-induced insulin resistance in mice lacking TNF-alpha function. Nature 389, 610–614.
[76] Arunachalam, S., Kim, S.Y., Kim, M.S., Yi, H.K., Yun, B.S., Lee, D.Y. and Hwang, P.H. (2012) Adriamycin inhibits adipogenesis through the modulation of PPARgamma and restoration of adriamycin-mediated inhibition of adipogenesis by PPARgamma over-expression. Toxicol. Mech. Methods 22, 540–546.
[77] Birsoy, K., Chen, Z. and Friedman, J. (2008) Transcriptional regulation of adipogenesis by KLF4. Cell Metab. 7, 339–347.
[78] Zhou, Q., Hong, Y., Zhan, Q., Shen, Y. and Liu, Z. (2009) Role for Kruppel-like factor 4 in determining the outcome of p53 response to DNA damage. Cancer Res. 69, 8284–8292.